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Multi-Disciplinary Clinical Study of Smith-Magenis Syndrome (Deletion 17p11.2)

Frank Greenberg, Richard A. Lewis, Lorraine Potocki, Daniel Glaze, Julie Parke, James Killian, Mary Ada Murphy, Daniel Williamson, Frank Brown, Robert Dutton, Charles McCluggage, Ellen Friedman, Marcelle Sulek, and James R. Lupski

Departments of Molecular and Human Genetics (F.G., R.A.L., L.P., J.R.L.), Pediatrics and Texas Children's Hospital (F.G., R.A.L., D.G., J.P., M.A.M., D.W., F.B., E.F., M.S., J.R.L.), Ophthalmology (R.A.L.), Neurology (D.G., J.P., J.K.), Radiology (R.D., C.M.), and Otolaryngology (E.F., M.S.), Human Genome Center (J.R.L.), Baylor College of Medicine, Houston, Texas

Smith-Magenis syndrome (SMS) is a multiple congenital anomaly, mental retardation (MCA/MR) syndrome associated with deletion of chromosome 17 band p11.2. As part of a multi-disciplinary clinical, cytogenetic, and molecular approach to SMS, detailed clinical studies including radiographic, neurologic, developmental, ophthalmologic, otolaryngologic, and audiologic evaluations were performed on 27 SMS patients. Significant findings include otolaryngologic abnormalities in 94%, eye abnormalities in 85%, sleep abnormalities (especially reduced REM sleep) in 75%, hearing impairment in 68% (approximately 65% conductive and 35% sensorineural), scoliosis in 65%, brain abnormalities (predominantly ventriculomegaly) in 52%, cardiac abnormalities in at least 37%, renal anomalies (especially duplication of the collecting system) in 35%, low thyroxine levels in 29%, low immunoglobulin levels in 23%, and forearm abnormalities in 16%. The measured IQ ranged between 20–78, most patients falling in the moderate range of mental retardation at 40–54, although several patients scored in the mild or borderline range. The frequency of these many abnormalities in SMS suggests that patients should be evaluated thoroughly for associated complications both at the time of diagnosis and at least annually thereafter. © 1996 Wiley-Liss, Inc.

KEY WORDS: REM sleep abnormalities, mental retardation, microdeletion, contiguous gene deletion, chromosome syndrome

INTRODUCTION

The Smith-Magenis syndrome (SMS) is a multiple congenital anomaly, mental retardation (MCA/MR) syndrome associated with deletion of chromosome 17 band p11.2. Since its original description in 1982, over 100 patients with SMS have been reported [Allen et al., 1991; Colley et al., 1990; Fan and Farrell, 1994; Finucane et al., 1993a,b, 1994; Fischer et al., 1993; Greenberg et al., 1991; Hamill et al., 1990; Lockwood et al., 1988; Masuno et al., 1992; Meinecke, 1993; Moncla et al., 1991; Patil and Bartley, 1984; Popp et al., 1987; Smith et al., 1982, 1986; Stratton et al., 1986; Zori et al., 1993]. The clinical phenotype has been well described and includes minor craniofacial anomalies (brachycephaly, prominent forehead, synophrys, epicanthal folds, broad nasal bridge, ear anomalies, and prognathism), brachydactyly, self-injurious behaviors (head banging, wrist-biting, onychotillomania, and polyembolokoilmania [Greenberg et al., 1991]), sleep disturbances, auto-amplexation (self-hugging) stereotypy, signs of peripheral neuropathy (decreased deep tendon reflexes, decreased sensitivity to pain, pes cavus or planus), speech delay, and variable degrees of mental retardation. Less commonly reported are cleft lip and/or palate, congenital heart defects, seizures, hearing impairment, and urinary tract anomalies. The diagnosis of SMS is usually secured by cytogenetic analysis during the evaluation of developmental delay and/or congenital anomalies. However, in older individuals the phenotype is distinctive enough that a diagnosis can be made by an experienced clinician prior to cytogenetic confirmation.

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Frank Greenberg is now at Diagnostic Development Branch, National Center for Human Genome Research, NIH, Bethesda, MD.

Julie Parke is now at Department of Neurology, University of Oklahoma Health Science Center, Oklahoma, City, OK.

Address reprint requests to Dr. James R. Lupski, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Room 609E, Houston, TX 77030.

Since 1989, two authors (F.G., J.R.L.) fostered a clinical and molecular study of SMS patients after the demonstration that DNA markers linked to the gene for Charcot-Marie-Tooth disease type 1A (CMT1A) were deleted in SMS patients and in mouse/human hybrids retaining the del(17)(p11.2) chromosome derived from SMS patients [Greenberg et al., 1991; Guzzetta et al., 1991, 1992]. To correlate the clinical, cytogenetic, and molecular findings of SMS patients, we embarked on a multi-disciplinary study of del(17)(p11.2) patients. This project intended to define the clinical spectrum (including laboratory and diagnostic imaging) of the phenotype of patients with Smith-Magenis syndrome. The patients were evaluated for thyroxine, thyroid stimulating hormone, and immunoglobulin blood levels, peripheral neuropathy, sleep disturbances, speech and language disorders, hearing impairment, otolaryngologic, ophthalmologic, cardiac, brain, and renal abnormalities, and general development.

MATERIALS AND METHODS

Patient Ascertainment

Patients were enrolled in the study after high resolution cytogenetic analysis had demonstrated deletion of 17p11.2. Patients were solicited from Houston hospitals (Texas Children's Hospital, Ben Taub General Hospital, and Hermann Hospital) and from regional and national clinical geneticists and cytogeneticists. Transportation for the patient and one parent or guardian was provided through private funding. Informed consent was obtained prior to enrollment in the study and for specific procedures throughout the evaluation (e.g., nerve conduction tests and sleep studies). The patients were admitted to the General Clinical Research Center for children (GCRC) at Texas Children's Hospital for a four day evaluation.

Study Protocol

Evaluations included physical examination (F.G. or J.R.L.), anthropometrics (F.G. or J.R.L.), sleep and behavioral history, CBC and differential, thyroid function studies (T4, TSH), BUN, serum creatinine, serum immunoglobulins, urinalysis, ophthalmic examination (R.A.L.), electrodiagnostic studies (nerve conduction velocities) (J.P., J.K.), radiographic surveys (chest, spine, arms, hands), audiometrics, otolaryngologic evaluation (E.M.F., M.S.), developmental assessment (M.A.M., D.W., F.B.), speech and language evaluation, vocalization studies, polysomnography (D.G.), computed tomography or magnetic resonance imaging of the brain (C.M.), renal ultrasound, ECG, and echocardiogram (if indicated by clinical amamnesis). Medications which could interfere with the interpretation of the polysomnography and EEG were discontinued prior to these studies. In addition, venous blood was drawn from the patient and available parents for molecular analyses. Parental blood chromosomes were also studied if not documented previously. Unfortunately, not all patients consented to all studies, and in some cases the patients were not cooperative enough to complete selected investigations.

RESULTS

Study Demographics

Between January 1, 1990, and April 1, 1994, 29 patients were evaluated. Several of the del(17)(p11.2) subjects were reported previously, including two affected children with apparent chromosomal mosaicism [Finucane et al., 1993b; Juyal et al., 1995a,b]. These subjects (patients 540 and 641) were shown subsequently to be non-mosaic by FISH and are included in this report. Also included is the patient reported by Zori et al. [1993]: a girl with del(17)(p11.2) whose mother is mosaic for the deletion. The mother's phenotype is normal, and she is not included in our data analysis. In addition, a boy carrying a 12;17 translocation with the breakpoint in 17p11.2 [patient 360 in Greenberg et al., 1991] and mild behavioral manifestations of SMS was evaluated but is not included in these analyses because of his predominantly normal phenotype. Thus, 27 SMS patients, 9 males and 18 females, are summarized here. The mean age at examination was 9.2 ± 8.6 years with the median age of 6.5 years and a range of 1–30 years. Except for the one patient with the chromosomally mosaic mother, these patients had apparently de novo deletions as confirmed by normal parental blood chromosomes. All patients were ascertained in the United States. Findings are summarized as Table I. Typical physical findings are shown in Figures 1 and 2.

Developmental Assessment

The patients were studied with several age-appropriate psychometric tests (Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, Wechsler Intelligence Scale for Children-Revised, Wechsler Adult Intelligence Scale, Vineland Adaptive Behavior Scales, and Woodcock-Johnson Psychoeducational Battery Revised). The summary of the level of function is shown as Table II. The tested developmental or intelligence quotients ranged between 20 and 78, with most falling between 40 and 54 (Table III). In speech and language development, expressive language appeared substantively more delayed than receptive language.

TABLE I. Summary of Clinical Findings

	Abnormal/ total tested	Percent abnormal
Otolaryngologic examination	16/17	94
Ophthalmologic examination	23/27	85
Sleep study	18/24	75
Audiology examination	17/25	68
Scoliosis survey	13/20	65
Head CT	13/25	52
Echocardiogram	5/12	42
Renal ultrasound	9/26	35
Thyroxin (T4)	7/24	29
Immunoglobulins	3/13	23
Electroencephalogram	5/24	21
Forearm X-ray	3/19	16
Thyroid stimulating hormone (TSH)	2/24	8
Nerve conduction velocity	2/25	8
Electrocardiogram	1/17	6
Chest X-ray	1/23	4

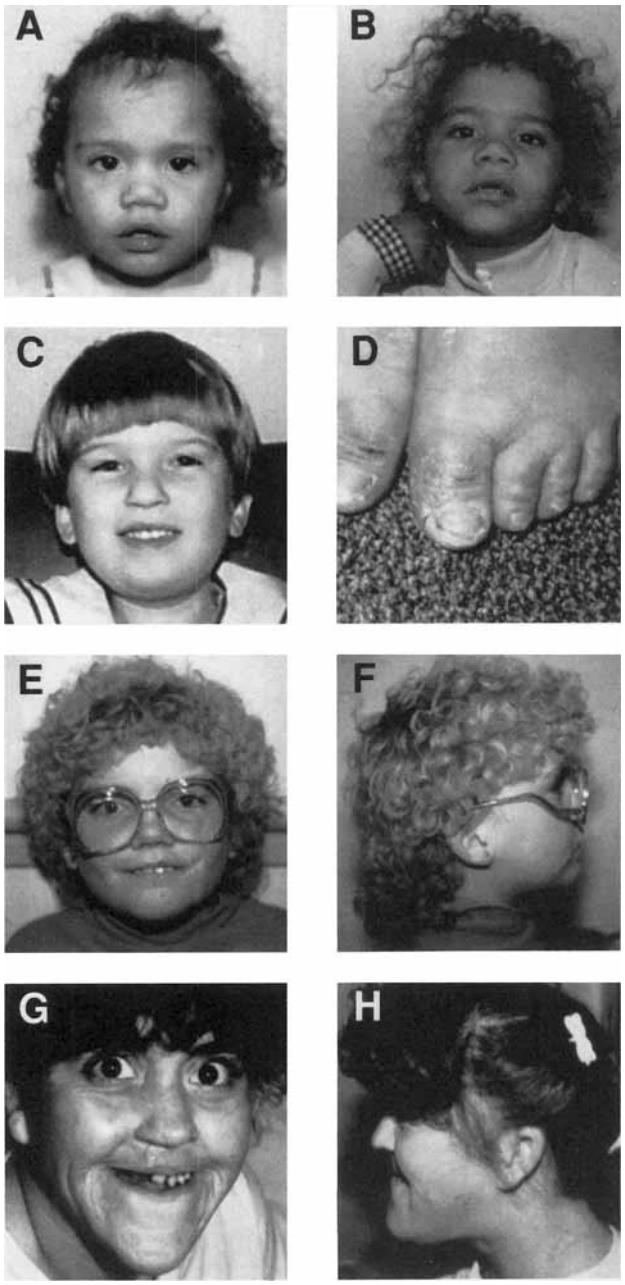

Fig. 1. Four patients with SMS. **A,B:** Patient 280 at 2½ years and 4 years of age. Note the flattened nasal bridge and down-turned upper lip. **C:** Seven-year-old girl, patient 641. The face is broad with midface hypoplasia and slight facial asymmetry. This patient has a smaller deletion than is usually observed in SMS [Juyal et al., 1995a]. **D:** Example of onychotillomania. **E,F:** Fourteen-year-old girl, patient 255. The face is broad with midface hypoplasia and slight prognathism. The ears are low-set and posteriorly rotated. **G,H:** Twenty-nine-year-old woman, patient 761. The head is brachycephalic, with prognathism; repaired cleft lip, and low-set, posteriorly rotated ears with overfolded helices.

Neurological Studies

Polysomnography could be performed on only 24 of the 27 patients. It was declined by two parents and could not be completed in only one patient because of lack of cooperation. Reduced REM sleep was noted in 12/24 patients and normal REM sleep in 11/24. One patient had slightly increased REM sleep percentages. Seven of the twenty-four patients had reduced sleep time. Since an EEG is done as part of the sleep study, five patients were noted to have epileptiform patterns without a clinical history of seizures.

Twenty-three of twenty-five patients had normal nerve conduction velocities. One patient (patient 200) had clinical evidence of severe peripheral neuropathy and wasting of the distal musculature of the legs [patient 2 of Smith et al., 1985]. He had slightly delayed motor nerve conduction velocities (median nerve = 35 m/sec; normal >40 m/sec). A nerve biopsy showed segmental demyelination and remyelination similar to that in Hereditary Neuropathy with Liability to Pressure Palsy (HNPP), but no tomaculous changes were identified. Another patient [(patient 484) Zori et al., 1993] had delayed conduction in the median nerves on two occasions but normal sensory conduction and normal conduction in other motor nerves. The *PMP22* gene is known to be deleted in this patient [Zori et al., 1993].

Ophthalmic Evaluations

Of the 27 patients who had complete eye examinations, only 4 had normal findings. Strabismus was noted in ten and myopia in ten. Ten patients had microcornea and sixteen had iris dysplasia. Two patients had nasal corectopia and one had an iris coloboma (without choroidal coloboma) in each eye.

Otolaryngologic Findings

Of the 25 patients who had audiometry evaluations performed, 10 had evidence of conductive hearing impairment, usually in the mild range, 5 had sensorineural loss, and 2 had a mixed loss. Of the 12 patients who had laryngoscopy, 8 were normal and 4 had various abnormalities including polyps, nodules, edema, or paralysis. Two of the twenty-two patients had evidence of repaired cleft palate. Each of these two individuals had hypernasal speech and velopharyngeal incompetence (VPI). Two additional patients without overt palatal clefts had VPI and hypernasal speech.

Diagnostic Imaging

Various noninvasive studies were performed to evaluate these patients for congenital malformations and other abnormalities. Twenty-five patients had imaging studies of the brain: nine evidenced ventriculomegaly; two had an enlarged cisterna magna; one had an enlarged foramen magnum; one had partial absence of the vermis and prominent cerebrospinal fluid spaces; one had dystrophic calcification of the right frontal lobe; and twelve were normal.

Echocardiograms were performed in 12 of the 27 patients. Five of these patients had abnormalities which included mild tricuspid regurgitation, mild mitral regurgitation, subvalvular aortic stenosis, ventricular septal defect, and supravalvular pulmonic stenosis with an atrial septal defect. Four patients who did not have an echocardiogram during this study had been evaluated previously and found to have either pul-

Fig. 2. Spectrum of craniofacial findings in SMS. **A,B:** Three-and-one-half-year-old girl, patient 541; **C,D:** 4-year-old boy, patient 895; **E,F:** 5-year-old girl, patient 280 (same patient in A,B in Fig. 1); **G,H:** 7-year-old boy, patient 656; **I,J:** 9-year-old girl, patient 725; **K,L:** 10-year-old girl, patient 898; **M,N:** 15-year-old boy, patient 540; **O,P:** 29-year-old man, patient 924. Some common anomalies represented are: brachycephaly, broad and flat facies, synophrys, strabismus, midface hypoplasia, downturned upper lip, prognathism, and malpositioned and/or malformed helices. The anomalies are more distinct in older individuals.

TABLE II. Level of Functioning

	Standard scores: mean 100; S.D. 15			
Scale	Number	Mean	S.D.	Range
Verbal	18	55.83	11.45	30–73
Performance	18	55.17	13.43	30–88
Overall cognitive	25	47.44	15.10	20–78
Adaptive behavior				
Composite	24	46.50	14.60	20–70
Communication	24	51.29	17.94	20–88
Daily living skills	24	44.33	19.53	20–77
Socialization	24	56.04	16.37	20–79
Motor skills	8	60.38	8.52	52–78

monic stenosis, a ventricular septal defect (repaired), a prolapsed mitral valve, or an atrial septal defect. One of 17 ECGs was abnormal and demonstrated a right ventricular conduction defect. Thus, at least 10 of 27 (37%) patients had a cardiac abnormality.

Of the 26 patients who had renal ultrasonography, 9 had abnormalities, including 4 patients with duplication of the collecting system, and 1 patient each with unilateral renal agenesis and ectopic kidney. One patient had bladder distension with residual noted by a voiding cystourethrogram.

Vertebral radiographs showed that 13 of 20 patients $\geq$ 4 years old had mild to moderate scoliosis, most commonly of the mid-thoracic region. Three of nineteen patients studied had short or bowed ulnae but none had radio-ulnar synostosis. All but one patient had a normal chest radiograph. The patient with supravalvular pulmonic stenosis and atrial septal defect had an enlarged cardiac silhouette.

Blood and Biochemical Analyses

All subjects had normal complete blood counts and urinalyses. One patient (540) who was known to have chronic renal disease [Finucane et al., 1993b] had an elevated serum BUN and creatinine, but all other patients had normal levels. Of 13 patients tested for immunoglobulin concentrations, 3 had mildly decreased levels and 1 had mildly elevated IgM. Of 24 patients in whom thyroid hormone levels were assayed, 7 had thyroxine levels below the normal range. One of those patients and also another patient with a normal T4 level had elevated TSH levels. No patient had overt hypothyroidism.

Other Anomalies

Although we are aware of SMS patients with other major malformations (including one with jejunal atresia and one with bladder extrophy), none of the patients in our series had any other known major malformations.

DISCUSSION

Since its first description in 1982, the clinical phenotype of Smith-Magenis syndrome, del(17)(p11.2), has been well delineated, including the minor anomalies, behavior characteristics, and sleep disorders. To correlate the clinical, cytogenetic, and molecular findings of SMS patients, we performed multiple clinical investigations in 27 patients. Some anomalies reported in SMS patients that are difficult to evaluate in an outpatient setting were investigated in this study, including evaluation of organ system development with noninvasive imaging and sleep pattern analysis. While the individual findings in these 27 patients with del(17)(p11.2) varied, all had typical phenotypic characteristics of SMS.

Our investigations confirmed the common clinical manifestations of SMS. Their frequency suggests that relevant investigations should be performed in the initial evaluation of SMS patients. For example, based on a single blood study, about one fourth of our tested patients have borderline hypothyroidism. This suggests that an explanation and understanding of this deficiency in SMS patients should be pursued. When one of our patients with a history of multiple infections early in life was found to have hypogammaglobulinemia, we added quantitative immunoglobulins to our study panel. Three of thirteen subsequent patients had decreased immunoglobulin levels, suggesting that this defect in SMS may merit further inquiry.

Among the radiographic studies, mild thoracic scoliosis was detected in 65% of patients $\geq$ 4 years old. While scoliosis had been noted previously in SMS [Greenberg et al., 1991], the prevalence was not known to be this

TABLE III. Range of Intellectual Levels

Number of subjects	Age range years	Level I.Q.	Range	Deviation below the mean
3	<1–11	Profound retardation	<25	5
4	6–12	Severe retardation	25–39	4
11	<2–16	Moderate retardation	40–54	3
6	7–29	Mild retardation	55–69	2
1	30	Borderline	70–79	1.3

high, although the greater number of females in our study may have skewed this prevalence. No patient required intervention for scoliosis. Of the 25 patients with brain imaging studies, 9 had ventriculomegaly, and 2 had enlarged cisterna magna, neither of which seems to have clinical significance. One patient had partial absence of the cerebellar vermis. Although brain abnormalities were reported previously in one individual [Masuno et al., 1992], these malformations do not appear common in SMS. Nine of twenty-six patients studied by renal ultrasound (35%) had abnormalities of the urinary tract, particularly duplication of the collecting system. One patient had unilateral renal agenesis and another had an ectopic kidney. Thus, the urinary tract should be investigated in all patients, especially those with urinary tract signs or symptoms. Although limited pronation and supination have been reported in SMS and a few patients were documented to have radio-ulnar synostosis [Greenberg et al., 1991], this observation was not confirmed here, although three patients did have short or bowed ulnae.

No single cardiac defect predominated among this group of SMS patients; however, 5 of 12 (42%) of the patients studied by echocardiogram under our protocol were found to have a valvular or structural abnormality. In addition, four patients studied previously were also known to have cardiac abnormalities. Conduction defects were not common. Given the high prevalence of cardiac abnormalities, we suggest that all SMS patients have an echocardiogram so that the true prevalence and spectrum of cardiac abnormalities can be ascertained.

Although myopia was reported in all 10 SMS patients in the study by Finucane et al. [1993a], only 30% of our patients exhibited myopia when they were evaluated. This difference might be related to differences in ages of assessment or to the sources of ascertainment. Regardless of the true prevalence of myopia, the overall high prevalence (85%) of ocular abnormalities warrants diligent ophthalmologic examinations annually in SMS patients. Further details regarding ophthalmic manifestations of SMS are described elsewhere [Chen et al., 1996].

Nearly half (48%) of the patients had mild conductive hearing impairment which was usually associated with a history of recurrent otitis media. Seven of our patients had sensorineural hearing impairment, which is of interest since a gene for one form of autosomal recessive hereditary deafness has been mapped to the SMS critical region [Friedman et al., 1995]. Two patients were known to have repaired cleft palate. However, well into the study, one of us (FG) observed that several patients had hypernasal speech. Two of these individuals were evaluated by modified barium swallow and found to have velopharyngeal incompetence (VPI). VPI and submucous cleft palate may be more common in SMS than previously recognized and may contribute to the speech pathology and frequent otitis media. This association deserves further study; early palatoplasty might be considered in management, depending on further investigations.

Although all the older patients had a typical deep hoarse voice noted previously in SMS [Greenberg et al., 1991], 8 of 12 patients had normal laryngoscopic findings. While 4 of 12 had various laryngeal defects, these may not necessarily account for the characteristic voice.

While the measured intelligence levels in the SMS patients varied, most individuals scored in the range of moderate mental retardation between 40 and 50. Most patients appeared to have less impaired receptive language ability when compared to expressive language skills. We hypothesize that the behavior of SMS patients might be related, in part, to frustration due to poor expressive language skills and that the use of sign language as an adjunct to speech therapy might not only improve language development but would also decrease the frustration associated with poor expressive language. This intervention may improve behavior and, if combined with treatment of VPI and speech pathology, would benefit the overall management of SMS patients.

Nearly 75% of the patients had clinical symptoms or signs associated with peripheral neuropathy which include one or more of the following: decreased deep tendon reflexes, decreased sensitivity to pain or temperature, or pes cavus or planus. However, only one patient (200) had clinically evident muscle wasting in the lower limbs and he was the only one to have slightly decreased nerve conduction velocities. Histological study of his sural nerve revealed segmental areas of demyelination and remyelination, consistent with Hereditary Neuropathy with Liability to Pressure Palsy (HNPP), although the characteristic tomaculous changes of HNPP were not observed [Chance et al., 1993]. HNPP is due to a deletion of the *PMP22* gene, the same gene that when duplicated causes most cases of Charcot-Marie-Tooth disease type 1A [Chance and Lupski, 1994; Chance et al., 1993, 1994; Le Geurn et al., 1994; Lorenzetti et al., 1995; Mariman et al., 1994a,b; Roa and Lupski, 1993, 1994; Silander et al., 1994; Verhalle et al., 1994]. Since HNPP may sometimes be associated with symmetrically delayed nerve conduction velocities, such may be the case in our patient 200 and may explain the unusual median motor conduction velocities of one SMS patient (484) with a larger deletion that includes *PMP22* [Zori et al., 1993]. The nerve conduction velocities in patients with HNPP can be normal; therefore some SMS patients may be deleted for *PMP22* but still have normal nerve conduction velocities. Current molecular studies of SMS patients show that most are not deleted for *PMP22* as the critical region is proximal to the usual CMT1A/HNPP duplication/deletion region [Greenberg et al., 1991; Chevillard et al., 1993; Moncla et al., 1993; our unpublished observations]. Therefore, the clinical signs of peripheral neuropathy in most SMS patients cannot be explained by deletion of *PMP22* and suggest that at least one other gene in the SMS critical region causes peripheral neuropathy.

The SMS critical region is estimated to contain at least 5 Mb of DNA or approximately 100 genes based on an average gene size of approximately 50 kb. Recently, a few genes that map within 17p11.2 and apparently in the SMS critical region have been identified [Chen et al., 1995; Chevillard et al., 19093; Hiraoka et al.,

1995; Hua et al., 1995; Zhao et al., 1995; unpublished observations of K.S. Chen and J.R. Lupski], but haploinsufficiency of any of these genes cannot explain the phenotype of SMS. Given the experience with the dosage-sensitive *PMP22* gene and the CMT1A/HNPP neuropathy phenotypes, it is likely that only a few genes mapping within the critical SMS deletion interval may contribute to the clinical phenotype.

The sleep disorder in SMS children is particularly disturbing to the families and also may be responsible for some behavioral problems. Patients have difficulty falling asleep and staying asleep and they awaken frequently during the night. In a previous report [Greenberg et al., 1991], two patients were noted to have absence of REM sleep. We completed sleep studies on 24 of the 27 patients. Half had reduced REM sleep but none had complete absence. Curiously, one patient had an increased percentage of REM sleep; 29% of patients had reduced sleep time secondary to frequent awakening. Thus, while a defect in REM sleep occurs in many SMS patients, the underlying cause of the sleep disorder is not apparent. However, a hypothetical gene within the critical region may affect REM sleep and thus sleep function.

Greenberg et al. [1991] reported that 30% of patients had seizures. In this series, three patients (11%) were reported to have seizures by history. Interestingly, none of these three patients was found to have EEG abnormalities. However, another 21% of the patients had epileptiform EEG patterns without a history of clinical seizures. The significance of this finding is unclear.

This study was designed as a survey, not as a therapeutic intervention; however, a comment about treatment is in order. Most patients had had a trial of medications to modify aberrant behavior. The most commonly prescribed medications were methylphenidate, pemoline, and thioridazine. In most cases, the stimulant drugs were not particularly effective in modifying behavior or improving attention span. Thioridazine caused excessive sedation in some patients. After an anecdotal report that the behavior of one patient with seizures improved while treated with carbamazepine, several patients were tried on carbamazepine even though they did not have clinically apparent seizure disorders. The behavior of many of these individuals improved while they took carbamazepine; however, the improvement was often transient. Until a formal treatment trial is conducted, carbamazepine therapy, including monitoring of blood levels, will be our first choice of therapy for severe behavioral problems in SMS. However, such treatments remain individual and several psychopharmacologic agents may need to be tested to find an optimal therapy for any SMS patient.

Based on these investigations, we suggest that every SMS patient should have annual evaluations for thyroid function, scoliosis, and ocular problems. Newly diagnosed patients should have a renal ultrasonography, audiologic evaluation, echocardiogram, assessment for velopharyngeal incompetence, and quantitative immunoglobulins. If any of these studies is abnormal, intervention and further clinical evaluation is appropriate. While the results of polysomnography, nerve conduction studies, and brain imaging have been academically intriguing, a survey of our data suggests that they are not necessary in every patient but may benefit individual clinical situations.

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REFERENCES

Allen WP, Phelan MC, Stevenson RE (1991): Smith-Magenis syndrome: Report of five patients. Proc Greenwood Genet Center 10:18–22.

Chance PF, Lupski JR (1994): Inherited neuropathies: Charcot-Marie-Tooth disease and related disorders. In Harding AE (ed): "Bailliere's Clinical Neurology. London: Baillière Tindall, pp 373–385.

Chance PF, Abbas N, Lensch MW, Pentao L, Roa BB, Patel PI, Lupski JR (1994): Two autosomal dominant neuropathies result from reciprocal DNA duplication/deletion of a region on chromosome 17. Hum Mol Genet 3:223–228.

Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B, Swanson PD, Odelberg SJ, Disteche CM, Bird TD (1993): DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 72:143–151.

Chen K-S, Gunaratne PH, Hoheisel JD, Young IG, Miklos GLG, Greenberg F, Shaffer LG, Campbell HD, Lupski JR (1995): The human homologue of the *Drosophila melanogaster* flightless-I gene (*fliI*) maps within the Smith-Magenis microdeletion critical region in 17p11.2. Am J Hum Genet 56:175–182.

Chen RM, Lupski JR, Greenberg F, Lewis RA (1996): Ophthalmic manifestations of Smith-Magenis syndrome (deletion 17p11.2). Ophthalmology (in press).

Chevillard C, Le Paslier D, Passage E, Ougen P, Billault A, Boyer S, Mazan S, Bachellerie JP, Vignal A, Cohen D, Fontes M (1993): Re-

lationship between Charcot-Marie-Tooth 1A and Smith-Magenis regions. *snU3* may be a candidate gene for the Smith-Magenis syndrome. Hum Mol Genet 2:1235–1243.

Colley AF, Leversha MA, Voullaire LE, Rogers JG (1990): Five cases demonstrating the distinctive behavioural features of chromosome deletion 17(p11.2p11.2) (Smith-Magenis syndrome). J Paediatr Child Health 26:17–21.

Fan YS, Farrell SA (1994): Prenatal diagnosis of interstitial deletion of 17(p11.2p11.2) (Smith-Magenis syndrome). Am J Med Genet 49: 253–254.

Finucane BM, Konar D, Haas-Givler B, Kurtz MB, Scott Jr CI (1994): The spasmodic upper-body squeeze: A characteristic behavior in Smith-Magenis syndrome. Dev Med Child Neurol 36:78–83.

Finucane BM, Jaeger ER, Kurtz MB, Weinstein M, Scott Jr CI (1993a): Eye abnormalities in the Smith-Magenis contiguous gene deletion syndrome. Am J Med Genet 45:443–446.

Finucane BM, Kurtz MB, Babu VR, Scott Jr CI (1993b): Mosaicism for deletion 17p11.2 in a boy with the Smith-Magenis syndrome. Am J Med Genet 45:447–449.

Fischer H, Oswald HP, Duba HC, Doczy L, Simma B, Utermann G, Haas OA (1993): Constitutional interstitial deletion of 17(p11.2) (Smith-Magenis syndrome): A clinically recognizable microdeletion syndrome: Report of two cases and review of the literature. Klin Padiatr 205:162–166.

Friedman TB, Liang Y, Weber JL, Hinnant JT, Barber TD, Winata S, Arhya IN, Asher Jr JH (1995): A gene for congenital, recessive deafness *DFNB3* maps to the pericentromeric region of chromosome 17. Nat Genet 9:86–91.

Greenberg F, Guzzetta V, Montes de Oca-Luna R, Magenis RE, Smith ACM, Richter SF, Kondo I, Dobyns WB, Patel PI, Lupski JR (1991): Molecular analysis of the Smith-Magenis syndrome: A possible contiguous-gene syndrome associated with del(17)(p11.2). Am J Hum Genet 49:1207–1218.

Guzzetta V, Montes de Oca-Luna R, Lupski JR, Patel PI (1991): Isolation of region-specific and polymorphic markers from chromosome 17 by restricted *Alu* polymerase chain reaction. Genomics 9:31–36.

Guzzetta V, Franco B, Trask BJ, Zhang H, Saucedo-Cardenas O, Montes de Oca-Luna R, Greenberg F, Chinault AC, Lupski JR, Patel PI (1992): Somatic cell hybrids, sequence-tagged sites, simple repeat polymorphisms, and yeast artificial chromosomes for physical and genetic mapping of proximal 17p. Genomics 13:551–559.

Hamill MA, Roberts SH, Maguire MJ, Laurence KM (1988): Interstitial deletion of 17p11.2: Case report and review. Ann Genet 31: 36–38.

Hiraoka LR, Hsu L, Hsieh C-L (1995): Assignment of *ALDH3* to human chromosome 17p11.2 and *ALDH5* to human chromosome 9p13. Genomics 25:323–325.

Hua X, Wu J, Goldstein JL, Brown MS, Hobbs HH (1995): Structure of the human gene encoding sterol regulatory element binding protein-1 (*SREBF1*) and localization of *SREBF1* and *SREBF2* to chromosomes 17p11.2 and 22q13. Genomics 25:667–673.

Juyal RC, Greenberg F, Mengden GA, Lupski JR, Trask BJ, van den Engh G, Lindsy EA, Christy H, Chen K-S, Baldini A, Shaffer L, Patel PI (1995): The Smith-Magenis syndrome deletion: A case with equivocal cytogenetic findings resolved by fluorescence in situ hybridization. Am J Med Genet 58:286–291.

Juyal RC, Finucane B, Shaffer LG, Lupski JR, Greenberg F, Scott CI, Baldini A, Patel PI (1995b): Apparent mosaicism for del(17)(p11.2) ruled out by fluorescence in situ hybridization in a Smith-Magenis patient. Letter to the editor. Am J Med Genet 59:406–407.

Le Guern E, Sturtz F, Gugenheim M, Gouider R, Bonnebouche C, Ravisé N, Gonnaud P-M, Tardieu S, Bouche P, Chazot G, Agid Y, Vandenberghe A, Brice A (1994): Detection of deletion within 17p11.2 in 7 French families with hereditary neuropathy with liability to pressure palsies (HNPP). Cytogenet Cell Genet 65:261–264.

Lockwood D, Hecht F, Dowman C, Hecht BK, Rizkallah TH, Goodwin TM, Allanson J (1988): Chromosome subband 17p11.2 deletion: A minute deletion syndrome. J Med Genet 25:732–737.

Lorenzetti D, Pareyson D, Sghirlanzoni A, Roa BB, Abbas NE, Pandolfo M, Di Donato S, Lupski JR (1995): A 1.5-Mb deletion in 17p11.2–p12 is frequently observed in Italian families with hereditary neuropathy with liability to pressure palsies. Am J Hum Genet 56:91–98.

Mariman ECM, Gabreëls-Festen AAWM, van Beersum SEC, Jongen PJH, van de Looij E, Baas F, Bolhuis PA, Ropers HH, Gabreëls FJM (1994a): Evidence for genetic heterogeneity underlying hereditary neuropathy with liability to pressure palsies. Hum Genet 93:151–156.

Mariman ECM, Gabreëls-Festen AAWM, van Beersum SEC, Valentijn LJ, Baas F, Bolhuis PA, Jongen PJH, Ropers HH, Gabreëls FJM (1994b): Prevalence of the 1.5-Mb 17p deletion in families with hereditary neuropathy with liability to pressure palsies. Ann Neurol 36:650–655.

Masuno M, Asano J, Arai M, Kuwahara T, Orii T (1992): Interstitial deletion of 17p11.2 with brain abnormalities. Clin Genet 41:278–280.

Meinecke P (1993): Confirmation of a particular but nonspecific metacarpophalangeal pattern profile in patients with the Smith-Magenis syndrome due to interstitial deletion of 17p. Am J Med Genet 45:441–442.

Moncla A, Piras L, Arbex OF, Muscatelli F, Mattei M-G, Mattei J-F, Fontes M (1993): Physical mapping of microdeletions of the chromosome 17 short arm associated with Smith-Magenis syndrome. Hum Genet 90:657–660.

Moncla A, Livet MO, Auger M, Mattei JF, Mattei MG, Giraud F (1991): Smith-Magenis syndrome: A new contiguous gene syndrome. Report of three new cases. J Med Genet 28:627–632.

Patil SR, Bartley JA (1984): Interstitial deletion of the short arm of chromosome 17. Hum Genet 67:237–238.

Popp DW, Johnson CP, Stratton RF (1987): An additional case of deletion 17p11.2. Am J Med Genet 26:493–495.

Roa BB, Lupski JR (1993): Molecular basis of Charcot-Marie-Tooth Disease type 1A: Gene dosage as a novel mechanism for a common autosomal dominant condition. Am J Med Sci 306:177–184.

Roa BB, Lupski JR (1994): Molecular Genetics of Charcot-Marie-Tooth neuropathy. In Harris H, Hirschhorn K (eds): "Advances in Human Genetics." New York: Plenum Press, pp 117–152.

Silander K, Halonen P, Sara R, Kalimo H, Falck B, Savontaus M-L (1994): DNA analysis in Finnish patients with hereditary neuropathy with liability to pressure palsies (HNPP). J Neurol Neurosurg Psychiatry 57:1260–1262.

Smith ACM, McGavran L, Waldstein G, Robinson J (1982): Deletion of the 17 short arm in two patients with facial clefts and congenital heart disease. Am J Hum Genet 34:A410.

Smith ACM, McGavran L, Robinson J, Waldstein G, Macfarlane J, Zonona J, Reiss J, Lahr M, Allen L, Magenis E (1986): Interstitial deletion of (17)(p11.2p11.2) in nine patients. Am J Med Genet 24:393–414.

Stratton RF, Dobyns WB, Greenberg F, DeSana JB, Moore C, Fidone G, Runge GH, Feldman P, Sekhon GS, Pauli RM, Ledbetter DH (1986): Interstitial deletion of (17)(p11.2p11.2): Report of six additional patients with a new chromosome deletion syndrome. Am J Med Genet 24:421–432.

Verhalle D, Löfgren A, Nelis E, Dehaene I, Theys P, Lammens M, Dom R, Van Broeckhoven C, Robberecht W (1994): Deletion in the CMT1A locus on chromosome 17p11.2 in hereditary neuropathy with liability to pressure palsies. Ann Neurol 35:704–708.

Zhao Z, Lee C-C, Jiralerspong S, Juyal RC, Lu F, Baldini A, Greenberg F, Caskey CT, Patel PI (1995): The gene for a human microfibril-associated glycoprotein is commonly deleted in Smith-Magenis syndrome patients. Hum Molec Genet 4:589–597.

Zori RT, Lupski JR, Heju Z, Greenberg F, Killian JM, Gray BA, Driscoll DJ, Patel PI, Zackowski JL (1993): Clinical, cytogenetic, and molecular evidence for an infant with Smith-Magenis syndrome born from a mother having a mosaic 17p11.2p12 deletion. Am J Med Genet 47:504–511.